Review article

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ENTERAL NUTRITION IN SEPSIS - CAN WE BREAK THE MYTH?

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Sepsis is a complex disorder that occurs as a result of the host's inadequate response to infection and it is associated with acute organ failure and a high mortality rate. Over the past 30 years lot of researches have been conducted in this field, which resulted in a faster recognition of the septic patient by using adequate scores and changing the existing ones. Septic shock is defined as hypotension despite adequate fluid resuscitation, therefore requires vasopressor support and is accompanied by circulatory, metabolic and cellular abnormalities.

Sepsis and septic shock are typically associated with catabolic stress where patients exhibit a systemic inflammatory response associated with complications such as multiorgan dysfunction, morbidity, prolonged hospitalization and death. Malnutrition is common in septic patients, taking into account pronounced catabolism in the early phase. In septic patients, enteral nutrition can be important for covering the energy requirements. Early nutrition therapy, primarily by enteral route, is today seen as a

proactive therapeutic strategy with the aim of reducing severity of the disease, complications, length of hospital stay and positive outcome of the patient.

Enteral nutrition should not be started in patients who are hypotensive (MAP<50mmHg), in whom treatment with vasopressors has just started or in whom there is an escalation of vasopressor doses. According to recommendations, enteral nutrition should be withheld until hemodynamic stability is achieved. The risks and benefits of enteral nutrition must be considered for each patient in the state of septic shock. Noradrenaline dose of <0.3mcg/kg/min can be considered safe and such patients can be characterized as hemodynamically stable.

Key words: sepsis, septic shock, enteral nutrition, vasopressors, noradrenaline

Pregledni rad

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ENTERALNA ISHRANA U SEPSI – DA LI MOŽEMO DA RAZBIJEMO MIT?

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Sepsa predstavlja kompleksni poremećaj koji nastaje kao posledica neadekvatnog odgovora domaćina na infekciju i povezana je sa akutnom organskom disfunkcijom i visokom smrtnošću. Tokom proteklih 30 godina, veliki broj straživanja je posvećen sepsi, što je rezultovalo bržim prepoznavanjem septičnog pacijenta korišćenjem adekvatnih skorova i menjanjem već postojećih. Septični šok se definiše kao perzistentna hipotenzija, refrektarna na nadoknadu tečnosti, koja zahteva upotrebu vazopresora, praćena cirkulatornim, metaboličkim i ćelijskim poremećajima.

Sepsa i septični šok su povezani sa kataboličkim stresnim odgovorom koji karakterše sistemski inflamantorni odgovor praćen komplikacijama kao što

su multiorganska disfunkcija, morbiditet, produženo bolničko lečenje i smrt. Malnutricija je česta kod septičnih pacijenata, uzimajući u obzir izražen katabolizam tokom akutne faze. Enteralna ishrana je važna u obezbeđivanju energetskih potreba ovih pacijenata. Rana ishrana, prvenstveno enteralnim putem, danas se posmatra kao proaktvna terapjska strategija sa ciljem redukovanja težine bolesti, smanjenja kompilkacija, dužine bolničkog lečenja i pozitivnog ishoda samog lečenja.

Sa enteralnom ishranom ne treba počinjati kod pacijenata koji su hipotenzivni (MAP<50mmHg), kod kojih se tek krenulo sa upotrebom vazopresora ili ukoliko se doza vazopresora eskalira. Prema preporukama, enteralna ishrana se treba zaustaviti do hemodinamske stabilizacije. Rizici i benefiti enteralne ishrane moraju se uzeti u obzir za svakog pojedinačnog pacijenta u stanju septičnogšoka. Noradrenalin u dozi<0,3mcg/kg/min se smatra bezbednim i takav pacijent se može okarakterisati kao hemodinamski stabilan.

Ključne reči: sepsa, septični šok, enteralna ishrana, vazopresori, noradrenalin

Introduction

Sepsis is a complex disorder that occurs as a result of the host's inadequate response to infection and it is associated with acute organ failure and a high mortality rate (1). It is very important health problem and requires urgent recognition and treatment because any delay reduces the survival rate. Over the past 30 years lot of studies and researches have been conducted in this field, which resulted in a faster recognition of the septic patient by using adequate scores and changing the existing ones (2,3). In 2017, World Health Organization declared sepsis a health priority and adopted concerning the improvement of prevention, diagnosis and treatment (4)

Starting in 1992, the definition of sepsis underwent many revisions, since it was then defined as an inflammatory response to infection. The clinical diagnosis was based on 2 or more criteria (hypo/hyperthermia, leukocytosis/leucopenia, heart rate>90/min, respiratory rate>20/min) of Systemic Inflammatory Response (SIRS) with a suspected or confirmed source of infection (5). At that time, septic shock was defined as persistent hypotension and hyperlactatemia refractory to fluid resuscitation. Considering that these definitions lacked both the sensitivity and specificity, in 2001 a criterion for organ dysfunction evaluation (SOFA) score was introduced, which indicated severe sepsis (6).

After about two decades, in 2016, the Third International Consensus on the Definition of Sepsis and Septic Shock defined sepsis as a life-threatening

organ dysfunction which occurs as a result of an inadequate host response to infection, and septic shock as a sepsis accompanied by circulatory, metabolic and cellular abnormalities (7). Clinically, shock is defined as persistent hypotension accompained by MAP<65mmHg ad increased serum lactates >2mmol/L after fluid resuscitation. Also, septic shock is accompanied by higher mortality rate, of 40%, which is in the case of sepsis about 10% (1).

The importance of nutrition in hospital conditions should not be neglected. Critical illness, including sepsis and septic shock is typically associated with catabolic stress where patients exhibit a systemic inflammatory response associated with complications such as multiorgan dysfunction, morbidity prolonged hospitalization and death. Malnutrition is common in septic patients, taking into account pronounced catabolism in early phase. In this case, enteral nutrition (EN) which delivers nutrients into the digestive system can be important for covering the energy requirements of these patients (8).

In the last three decades, great progress has been made in understanding the molecular and biological effects of nutrients in maintaining homeostasis in critically ill patients. Traditionally, nutrition support meant an additional form of treatment and patient care with the goal of providing enough energy to maintain lean body mass. Recently, this type of therapy has been called *nutritional therapy*, which implies support in maintaining a normal metabolic

response to stress, prevention of oxidative cell damage and positive impact on immune response (9).

Early nutrition therapy, primarily by enteral route (EEN), is today seen as a proactive therapeutic strategy with the aim of reducing severity of the disease, reducing complications, length of hospital stay and positive outcome of the patient.

Based on expert's opinions, comorbidities, the condition and function of the digestive system, as well as the risk of aspiration should be taken into account within the nutrition assessment. Traditional serum markers, albumin, prealbumin, transferin, retinol-binding protein, as indicators of the acute inflammatory phase are no longer recommended in the Intensive Care Unit (ICU) (10). For determining energy requirements, the indirect calorimetry is an option, whenever is available. If it is not available, ESPEN (European Society for Parenteral and Enteral Nutrition), ASPEN (American Society for Parenteral and Enteral Nutrition) and SCCM (Society for Critical Care Medicine) recommend to use predictive equations based on patient's body weight (25-30kCal/kg/day) (9, 11, 12).

The most important macronutrients are proteins, necessary for wound and anastomoses healing, to support the immune system and maintain the lean body mass. For the majority of critically ill patients, the need for proteins is greater than daily energy requirements, and they often cannot be met

with EN only, especially in first days of illness. Patients with frequent interruption of EN may benefit from protein supplementation. Daily needs of protein are about 1.2-2gr/kg/day (9,11, 12).

Recommendations for starting early EN are within 24-48h of admission in the ICU (9, 11, 12). Enteral nutrititon maintains the integrity of gastrointestinal tract and strong junctions between epithelial cells, promotes blood flow through mucosa, stimulates the throphic factors release (cholecystokinn, gastrin, bombesin and bile salts). It also stimulates the secretion of IgA (13-15).

Patients with septic shock are special group of critically ill patients and EN in these patients is recommended with great caution. The reason lies in fact that early EN may led to additional hemodynamic instability and can be cause of mesenteric ischemia and necrosis (9). In the early phase of shock, the blood flow is directed from splanchnic circulation to the vital organs, such as the brain, heart and lungs. This can result in intestinal dysfunction, which is considered to be the key in the development of sepsis-mediated multiorgan dysfunction by increasing the permeability of intestinal mucosa, bacterial translocation and systemic inflammation (16). Splanchnic hypoperfusion and inadequate oxygen utilization in cells result in significant pathophysiological disorders in digestive tract (enterocyte necrosis, overgrowth of pathogenic bacteria and their dislocation into the systemic circulation and disruption of local immune response) which can be

additionally enhanced by reperfusion and use of vasopressors (17-19). High doses of vasopressors can increase the already existing high metabolic and energy needs of endothelial cells (20-22). In septic patients, there is a subclinical ischemic/reperfusion damage as a result of intestinal microcirculation disorders. Intestinal ischemia due to use of EN is very rare but can be unrecognized and fatal (24). Retrospective studies in patients who are on stable doses of vasopressors have shown that early EN reduces length of hospital stay and mortality compared to late EN (25).

Enteral nutrition should not be started in patients who are hypotensive (MAP<50mmHg), in whom treatment with vasopressors has just started or in whom there is an escalation of vasopressor doses. In these patients signs of feeding intolerance should be especially monitored, and if they are present, the dose of EN should be reduced or discontinued (9).

According to recommendations, enteral nutrition should be withheld until hemodynamic stability is achieved (26-28). It is necessary to define hemodynamically stable and unstable patients, because EN increases cardiac output, decreases systemic vascular resistance and increases mesenteric blood flow. The concept of early EN implies the use of EN within 72h, and even 48h of admission. It is reasonable to continue with EN in patients who are on stable doses of vasopressors, assuming that the patent is hemodynamic stable and the MAP is >70mmHg (28). Current evidences and experts opinions are that the shock is not the contraindication for

enteral nutrition (9, 28). It is recommended to start with lower doses of EN in patients with controlled state of shock and who are on low or moderate doses of vasopressors (29-31). However, the exact doses of vasopressors are not clearly defined in clinical practice.

Although clinical studies have been shown the benefits of EN, the risk and benefit in patients with shock must be rationally evaluated. Enteral compared to parenteral nutrition lowers the risk of infection and length of hospital stay (32). However, the FRANS study showed that providing large amounts of macronutrients during the early phase of ICU stay can have negative impact (33). Studies NUTRIREA 2 and NUTRIREA 3 provided evidences in terms of reducing the risk of introducing EN in patients with shock, but early EN in hemodynamically unstable patients could have negative impact on patient's outcome (34, 35). This may be due to the fact that hyperinflammation, oxidative stress and mitochondrial dysfunction are present in the early stage of septic shock, while in the other hand, EN requires an increase of blood flow through gastric mucosa and can worsen an already existing poor visceral perfusion that accompanies the state of shock (36). Therefore, in patients who are hemodynamically stable and without need for vasopressor escalation, EN should be started with providing 20-50% of the estimated energy requirements and gradually increased while monitoring the tolerance of gastrointestinal tract of each individual patient.

Enteral nutrition should start with small, trophic doses (10-20ml/h or 500kCal/day) and gradually increase the dose by the end of first week. Trophic nutrition is sufficient to prevent atrophy and apoptosis of enterocytes and maintain the integrity of gastric mucosa. It is necessary to provide 50-60% of energy needs in order to reduce permeability of gastrointestinal mucosa and systemic inflammation. Using of gastric residual volume (GRV) as a sign of intolerance is still controversial, generally it is not recommended. If it is used in some ICUs, the guidelines recommends delaying EN if GRV is above 500ml/6h (9, 11).

Risk assessment of early EN in patients with septic shock

In patients with shock who are on vasopressors, early EN can additionally worsen already existing gastrointestinal dysfunction and even led to non-occlusive mesenteric ischemia or intestinal necrosis. Use of catecholamines during EN is a risk factor for intolerance (37). Use of sedatives, opiates, hyperglycemia, increased IAP (intra-abdominal pressure) and increased lactate levels are some of additional risk factors for intolerance (38). These factors should be carefully considered when deciding to initiate EN in patients on vasopressors. The risk of non-occlusive

mesenteric ischemia is greater when vasopressors are combined with inotropes (39, 40).

Safe threshold doses of vasopressors for initiating early EN

The German Nutrition Association suggests that EN can be harmful when the doses of noradrenaline are greater than 0.5mcg/kg/min (31). When using vasopressor score, ASPEN recommends that if it is >12, only trophic doses should be provided (9, 42). However, this score has not been proven in clinical practice.

Noradrenline has little effect on intestinal perfusion (43) but it can lead to flow redistribution. In animal models it has been shown that microcirculation through superior mesenteric artery, jejunum and pancreas is reduced during the infusion of noradrenaline and adrenaline (44). Adrenaline has also been proven to disrupt gastrointestinal perfusion in patients with shock (45) Otherwise, some authors believe that flow can be increased by increasing the cardiac output (46). The effects of dopamine depends on the dose. Lower doses increases and higher decreases flow through gastrointestinal mucosa (47, 48) Dobutamine increases (48-51) while vasopressin decreases flow (52,53)

By searching the data, it is indicated that starting EN is safe if noradrenaline doses are <0.3mcg/kg/min (54). Studies NUTRIREA 2 and NUTRIREA 3 suggest a threshold of 0.5mcg/kg/min (34, 35). For now, the

safe doses of vasopressors remain a matter of debate. It is important to emphasize that the state of shock is not a contraindication for starting EN. The risks and benefits of enteral nutrition should be considered for each patient in the state of septic shock. Noradrenaline dose of <0.3mcg/kg/min can be considered safe and such patients can be characterized as hemodynamically stable (9, 28).

Concluson

Sepsis and septic shock are no contraindications for the initiation of enteral nutrition. This type of nutrition is essential in maintaining

homeostasis, integrity and function of the gastrointestinal tract. For now there are no enough evidences to support clear benefits of early compared to delayed enteral nutrition. The complex effects of vasopressors on the gut must be considered when deciding when and which doses of nutrients should we start with. A norepnephrine dose <0.3mcg/kg/min are considered safe for starting EN in patients with septic shock. The risks and benefits of early EN should be weighted carefully for each critically ill patient.

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